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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/750,185 | 12/31/2003 | Sue K. DeNise | MMI-0101 (14972.105003) | 5843 |
| 20786 7590 07/09/2008 KING & SPALDING LLP 1180 PEACHTREE STREET ATLANTA, GA 30309-3521 | | | EXAMINER BAUGHMAN, MOLLY E | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--------------------------------------|--------------------------------------|--|
| Office Action Summary | Application No. 10/750,185 | Applicant(s) DENISE ET AL. | |
| | Examiner Molly E. Baughman | Art Unit 1637 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 April 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 24,25,33-35 and 40-51 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24-25, 33-35, and 40-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/15/08 has been entered.
2. Applicant's amendments to claims 24-25, 33-35, and 40-51, and cancellation of claims 1-23, 26-32 and 36-39 in the reply filed on 4/15/08 are acknowledged.
3. Claims 24-25, 33-35, and 40-51 are currently under examination.

Response to Arguments

4. Applicant's arguments, see pgs.5-7, filed 4/15/08, with respect to rejection of claims 24-25 and 33-51 under 35 USC § 112, second paragraph, particularly, parts a-h, have been fully considered and are persuasive. The rejection of claims 24-25 and 33-51 has been withdrawn. However, upon further consideration, new grounds of rejection under 35 USC § 112, second paragraph have been made in view of the amendments (see below).
5. Applicant's arguments, see pgs.7, filed 4/15/08, with respect to rejection of claims 24-25 and 33-51 under 35 USC § 112, first paragraph (written description), have been fully considered, but are not found persuasive. Applicants argued that

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amendments to the claims, particularly, removing language related to 90% identity has been removed, have limited the claims to a certain set of sequences in the bovine genome, specifically binding to the bovine genome. While this may have limited the claims to sequences within the bovine genome, the applicants have now amended the claims to include in part (a) of claim 24, a first polynucleotide which is capable of binding to a SNP position associated with the trait, tenderness, located in a region less than about 500,000 nucleotides from the nucleic acid residue 300 of SEQ ID NO:20614, and in part (b) of claim 24, an extension primer capable of binding to a target sequence adjacent to a SNP position located in a region less than about 500,000 nucleotides from the nucleic acid residue 300 of SEQ ID NO:20614, which in both cases, is not limited to the SNP at residue 300 of SEQ ID NO:20614 as claimed previously. As explained in the previous rejection, the position of SEQ ID NO:20614 in the bovine genome, or in relation to any other SEQ ID, or contig noted in the specification is not defined, and therefore, represents an indefinite number of possibilities for SNPs within 500,000 nucleotides from the nucleic acid residue 300 of SEQ ID NO:20614. The instant specification teaches SEQ ID NO: 20614. Tables 1A and 1B identify SEQ ID NO: 20614 to be sequences 742-1341 of contig 19866881037958, however, nowhere in the specification does it define where this contig is located in position to any other contig or within the bovine genome. There is no description or drawing (map) which shows the layout of the contigs in relation to one other within the bovine genome. Therefore, it is unclear how one can even determine whether there are any other markers also associated with tenderness which are within 500,000 nucleotides from nucleic acid

residue 300 of SEQ ID NO:20614. Furthermore, Table 1B lists other contigs which are nearby to contig 19866881037958, however, none of these contigs are listed elsewhere in the table, which would provide evidence for a SNP or marker within each nearby contig and its associated traits.

Adequate written description requires more than a statement that the SNPs of the invention are within 500,000 nucleotides that are associated with the same trait. The specification only provides support for the SNP located at residue 300 of SEQ ID NO:20614. The specification states that “***it is expected*** that other SNPs ***can be identified*** that are associated with the same traits based on the fact that these other SNPs are located less than or equal to about 500,000 nucleotides of the identified associated SNP on the bovine genome” (paragraphs [0035] and [0131]). Therefore, the applicants are not in possession of the SNPs being claimed, i.e. located in a region less than about 500,000 nucleotides from the nucleic acid residue 300 of SEQ ID NO:20614. A more detailed description of each SNP, comprising its location within the bovine genome is required.

In conclusion, the limited information provided is not deemed sufficient to reasonably convey to one skilled in the art that there are SNPs associated with tenderness located in a region less than about 500,000 nucleotides from the nucleic acid residue 300 of SEQ ID NO:20614 as claimed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

6. Applicant's arguments, see pg.7, filed 4/15/08, with respect to rejection of claims 37-39 under 35 USC § 112, first paragraph (written description), have been fully considered and are persuasive since the claims have been cancelled. The rejection of claims 37-39 has been withdrawn.

7. Applicant's arguments, see pg.7, filed 4/15/08, with respect to rejection of claims 24-25 and 33-51 under 35 USC § 112, first paragraph (enablement), have been fully considered, but are not found persuasive. Applicants argued that amendments to the claims, particularly, removing language related to 90% identity has been removed, have limited the claims to a certain set of sequences in the bovine genome, specifically binding to, or bind adjacent to, a specified SNP in the bovine genome. While this may have limited the claims to sequences within the bovine genome, the applicants have now amended the claims to include in part (a) of claim 24, a first polynucleotide which is capable of binding to a SNP position associated with the trait, tenderness, located in a region less than about 500,000 nucleotides from the nucleic acid residue 300 of SEQ ID NO:20614, and in part (b) of claim 24, an extension primer capable of binding to a target sequence adjacent to a SNP position located in a region less than about 500,000 nucleotides from the nucleic acid residue 300 of SEQ ID NO:20614, which in both cases, is not limited to the SNP at residue 300 of SEQ ID NO:20614 as claimed previously. Therefore, a scope of enablement for any SNPs other than that at position 300 of SEQ ID NO:20614 now applies.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention

The claims are drawn to sequences which are capable of binding to, or binding adjacent to, a SNP position associated with the trait, tenderness, located in a region less than about 500,000 nucleotides from the nucleic acid residue 300 of SEQ ID NO:20614. The invention is in the class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

As explained above under the written description rejection, the claims encompass an infinite number of possibilities of SNPs located in a region less than about 500,000 nucleotides from the nucleic acid residue 300 of SEQ ID NO:20614, as well as the SNP located at residue 300 of SEQ ID NO:20614. Since the specification does not adequately describe any sequences, let alone SNPs, within sequences located in a region less than about 500,000 nucleotides from the nucleic acid residue 300 of

SEQ ID NO:20614, this results in an enormous number of sequence possibilities and SNPs in the scope of the claim.

Quantity of Experimentation

The quantity of experimentation in this area is very large since there is significant variability in the effects of polymorphisms on phenotypes such as bovine meat tenderness. Screening each possible polymorphism in the bovine genome represents an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al (The Scientist (2004) Vol 18) titled his article "Gene Association Studies Typically Wrong" and states "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of printout)." This is consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) who notes that "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives (see abstract). Ioannidis (Nature genetics (2001) 29:306-309) further

supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see abstract, for example).

Even the art associated with identifying bovine SNP markers for trait characterization, demonstrates the unpredictability of polymorphism association. Heaton et al. ("Selection and use of SNP markers for animal identification and paternity analysis in U.S. beef cattle," Mammalian Genome, 2002, Vol.13, pp.272-281) state that SNP markers and can be used for association mapping to identify chromosomal regions containing loci involved with phenotypic traits and has been advocated as a method for mapping, however, a significant problem is the potential for spurious associations (i.e. false positives) that arise from unrecognized population stratification or recent admixture (page 279, 2nd column, 2nd paragraph). Heaton also states that at least 34 SNPs would be required to identify all 270,000 cattle registered by the American Angus Association, 40 SNPs for all of the 100 million cattle in the U.S., and 43 SNPs would be required for all of the 10 million cattle ever registered by the American Angus Association.

Therefore, it is highly unpredictable whether some currently unknown polymorphism in the bovine genome would have any association with any phenotype. Furthermore, one SNP cannot be used solely to identify a particular phenotype or genotype.

Working Examples

The specification has working examples where in Example 2, it explains that the SNP markers identified reach a threshold test statistic of 46.96294 for the trait of

tenderness and 21.66599 ($P < .01$) for the remaining four traits of retail yield, daily gain, fat thickness, and marbling were identified as associated SNPs and are listed in Tables 1A and 1B. There are no examples of any other sequences other than those in Tables 1A and 1B, which are shown to be associated with a trait.

Guidance in the Specification.

The specification does not provide sufficient evidence to demonstrate the association of polymorphisms being associated with a particular trait outside of those located at position 300 of each of SEQ ID NO: 19473-21982. The specification states that “***it is expected*** that other SNPs ***can be identified*** that are associated with the same traits based on the fact that these other SNPs are located less than or equal to about 500,000 nucleotides of the identified associated SNP on the bovine genome” (paragraphs [0035] and [0131]). Therefore, it does not adequately describe the association of such unknown SNPs within 500,000 nucleotides of position 300 of SEQ ID NO:20614 with tenderness. Tables 1A and 1B describe “nearby sequences” to SEQ ID NO:20614 (and MMBT07944), however, nowhere in the specification are SNPs identified and/or described in such nearby sequences. Additionally, in Table 1B, it states that MMBT07944 is sequences 742-1341 of contig 19866881037958, however there are no other sequences in Table 1B shown to be a “nearby sequence” of this contig, and other sequences nearby that SNP do not necessarily associate with the same trait. For example, other polymorphisms also associated with meat tenderness in Tables 1A and 1B, such as MMBT02858, MMBT16580, MMBT21179, MMBT05003, MMBT18802, MMBT18799, and MMBT18797, are not a “nearby sequence” to MMBT07944. In a larger aspect, the specification provides no reference to where any of the sequences correspond to the bovine genome in order to determine the distance and position of

each sequence and how each SNP are positioned to each other. The sequences are related to particular “contigs” wherein the specification does not indicate where in the bovine genome such contigs are located and where they are located in respect to each other, and the particular SNPs listed in Tables 1A and 1B.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching gene association studies are highly unpredictable is demonstrated by Heaton, Lucentini, Wacholder and Ioannidis. The specification provides one with no written description or guidance that leads one to a reliable method where any SNP outside of position 300 of SEQ ID NO:20614 as claimed is shown to be associated with a particular trait. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art and specification recognized problems in the use of polymorphisms for phenotype identification and trait mapping as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of working examples which do not address the full scope of the claims at issue and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue

experimentation for one of skill in the art to perform the method of the claim as broadly written.

8. Upon further consideration, new grounds of rejection have been made under 35 USC § 112, first paragraph (written description) over claim 35.

New Grounds of Rejection

Claim Rejections - 35 USC § 112 (Second paragraph)

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 24-25, 33-35, and 40-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 24-25, 33-35 and 40-41 are vague and indefinite in the claim 24 for the limitation " a SNP located in a region less than about 500,000 nucleotides from the nucleic acid residue 300 of SEQ ID NO: 20614", because the specification does not provide a limiting definition of any SNP or additional sequence in the bovine genome or contig that is associated with any trait as broadly encompassed by the claims. The metes and bound of the claims are unclear in the context of the SNP location and the binding regions for the first polynucleotide and extension primer. Thus a clear interpretation of Applicant's intent cannot be ascertained.

Claim Rejections - 35 USC § 112 (Written Description)

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As noted above, applicants fail to comply with the written description requirement of these claims for SNPs other than position 300 of SEQ ID NO:20614, and therefore, only the SNP at position 300 of SEQ ID NO:20614 will be addressed in this written description rejection.

Claim 35 encompasses a nucleotide occurrence for the SNP at position 300 of SEQ ID NO:20614 being associated with a bovine subject having a value for tenderness that is within ***at least 99th percentile*** of the bovine population. While applicants have support for a nucleotide occurrence being associated with bovine subject having a value for tenderness that is within 90th percentile of the bovine population, it does not provide adequate description of any nucleotide occurrence for this particular SNP to be associated with a bovine subject having a value for tenderness at any value above 90th percentile of the bovine population (see paragraphs [0057-0060] and [0198] of the specification). The specification states in paragraph [0060] that it is inferred that a

bovine subject has a significant likelihood of having a value for a trait that is 95th percentile of bovine subjects for a given trait, however, there is no data to support this allegation. The specification states that the SNPs in Tables 1A and 1B (including the instant SNP at position 300 of SEQ ID NO:20614) have particular nucleotide occurrences found to be in association with bovine subjects having particular values for tenderness, where a “high” value refers to those reaching 90th percentile of that phenotypic measurement based on numeric ranking for the trait. Therefore, based on the specification, one can only *infer* that any nucleotide occurrence for the SNP at position 300 of SEQ ID NO:20614 is associated with a bovine subject having a value for tenderness that is within 90th percentile of the bovine population for tenderness.

Summary

13. No claims are in condition for allowance.
14. It is noted that in the examiner’s attempts to search a representative number of nearby or adjacent sequences to the SNP at position 300 of SEQ ID NO:20614, as per part (b) of claim 24, the examiner carried out a search on SEQ ID NOs: 23124, 47083, 47087, 47089, 47091, 47093, 47096, 47098, 47102, and 47105 (a total of 10 sequences). Although the claims have indefiniteness issues to the possibilities of sequences which are nearby to SEQ ID NO:20614 in the bovine genome, in the scope of the claim being only limited to those in the specification, particularly those listed in

Tables 1A and 1B being "nearby sequences" to SEQ ID NO:20614, the sequences that were searched above are free of the prior art.

15. As noted previously, SEQ ID NO:20614 is also free of the prior art.

16. Any remaining rejections and/or objections not addressed above are withdrawn in view of the amendments and/or arguments.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is (571)272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CYNTHIA WILDER/
Patent Examiner, AU 1637

Molly E Baughman
Examiner
Art Unit 1637